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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,879	07/25/2003	Jang Han	072121-0189-Reg	1049

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
01/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,879	HAN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,2,4-7,10,13-15,17-20,24,25,28-30,32-35,38 and 42-81 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,2,4-7,10,13-15,17-20,24,25,28-30,32-35,38 and 42-81 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 1-23-07, 11-22-06, 11/14/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: Seq alignment data.

DETAILED ACTION

The Sequence Compliance Notice mailed 8-7-07 is hereby vacated in light of the amendments filed 11-1-04.

This Office action is in response to the communication filed 5-15-07.

Claims 1, 2, 4-7, 10, 13-15, 17-20, 24, 25, 28-30, 32-35, 38, 42-81 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Applicant's election with traverse of the 5'UTR of hepatitis C virus genome, siRNA5 in the reply filed on 5-15-07 is acknowledged. The traversal is on the ground(s) that the different sequences or target regions claimed share a common function and structural feature in that all of the recited sequences target conserved domains necessary for HCV replication, there is no serious burden on the Examiner to search all of the target regions, and all of the sequences claimed have already been searched and examined. This is not found persuasive because each of the siRNA targeting a different region of the HCV genome comprises a different and distinct sequence and so is chemically and structurally distinct and different, each targets a different region with different specificity and efficiency and therefore is biologically and functionally distinct, and therefore each siRNA molecule is patentably distinct. Furthermore, the searches required to properly examine all of the siRNA sequences claimed, which are directed to

different regions of the genome, would pose a serious burden on the Examiner and one search would not be coextensive with the searches required for the other siRNA sequences, although they may overlap. Furthermore the data bases that must be searched are extensive for each particular sequence claimed.

The requirement is still deemed proper and is therefore made FINAL.

SiRNA targeting the regions other than the 5'UTR and siRNA5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5-15-07.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1, 2, 4-7, 10, 13-15, 17-20, 24, 25, 28-30, 32-35, 38, 42-81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed on 5-23-06.

The claims are drawn to compositions and methods of inactivating HCV in a patient comprising administration of an siRNA molecule that targets various regions of the genome of HCV and inactivates the virus, which siRNA molecules are optionally modified, and which optionally are at least 80% identical to the target HCV genome.

Applicant's arguments filed 11-22-06 have been fully considered but they are not persuasive. Applicant argues that adequate written description has been provided for the broad genus of siRNA compounds claimed because a representative number of species have been shown to provide for the genus claimed, and the subject matter shares a common attribute, which is that all of the claimed sequences relate to RNA molecules that target the various regions of the HCV genome.

Contrary to Applicant's assertions, the genus reads broadly on any siRNA that targets HCV in the various regions claimed, including species with non-homologous species (e.g. including 80% variance), and which siRNA inactivates or inhibits replication of HCV. The instant specification teaches the design of several siRNA molecules directed to various regions of the HCV genome (Fig 2) and the ability of several of these species, in modified and unmodified form, to inhibit HCV replication in vitro. These do not adequately represent the broad genus of compounds claimed, including non-homologous species, and which broad genus of compounds provide for the function claimed, of inactivating HCV in vitro and in vivo. The species taught in the instant specification are not representative of this broad genus of species claimed, comprising any siRNA which targets the various regions of the HCV genome listed in the claims and further whereby HCV replication is inhibited in vitro and in a subject.

One of skill in the art would reasonably conclude that the instant application, at the time of filing, did not provide adequate description of the genus of compounds claimed, encompassing any siRNA targeting the various regions spanning the HCV genome, or any homolog sharing at least 80% identity with the target region, whereby

upon administration provides for the function claimed, of inactivating HCV in vitro and in a subject.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-7, 10, 13-15, 17-20, 24, 25, 28-30, 32-35, 38, 42-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Wands et al (USPN 6,001,990) and Wakita et al (WO 95/30746) in view of Fire et al (USPN 6,506,559), Elbashir et al (EMBO J., vol. 20, No. 23, pages 6877-6888, 2001), Fosnaugh et al (US 2003/0143732), Morrissey et al (US 2003/0206887) and Tuschl et al (2002/0086356), the combination further in view of Noonberg et al Noonberg (USPN

5,624,803) and Baracchini et al (5,801,154) insofar as the claims are drawn to compositions and methods for inhibiting replication and inactivating HCV in vitro comprising the administration of an siRNA molecule that targets the 5' UTR of the HCV genome, or which siRNA comprises siRNA5, which siRNA is optionally modified at the 2' position with a methoxy or fluoro group, and further comprises a cholesterol moiety, or which siRNA is optionally in an expression vector comprising an H1 or U6 promoter, expressed as a single, self complementary molecule, or which sense and antisense strands are expressed from separate promoters.

Wands et al (USPN 6,001,990) teach the targeting and inhibition of HCV comprising the administration of inhibitory oligonucleotides (antisense) which are specific for the 5' UTR of the HPV genome (see SEQ ID No 12 and Acc No. AAZ57757 of US 6,001,990 and the accompanying sequence alignments; see col. 1-6, 9-10, 13-14).

Wakita et al (WO 95/30746) teach the targeting and inhibition of HCV comprising the administration of inhibitory oligonucleotides (antisense) which are specific for the 5' UTR of the HCV genome, including the region targeted by siRNA5. Wakita also teaches the role of HCV in various pathological conditions, and the targeting of liver cells with these inhibitory oligonucleotides (see pages 1-2, 5-6, 8, 16-20; see Acc No AAT05222 of Wachita and the accompanying sequence alignment data).

Fire et al (USPN 6,506,559) teach the use of various inhibitory oligonucleotides for inhibiting the expression of a known target gene. Fire also teaches the advantages of using siRNA oligonucleotides for target gene inhibition, including viral target genes,

which siRNA is optionally expressed in an appropriate expression for target cell delivery as either a single, double stranded molecule or as separate, complementary strands (see esp. col. 1-4, 6-7, claims 1, 5, 10 and 21).

The primary references of Wands, Wakita and Fire do not teach methods of generating 21-23 nucleotide length siRNA molecules in the presence of dicer, nor the incorporation of 2'-fluoro or 2'-alkyloxy modified groups into the siRNA molecules, or siRNA further comprising cholesterol groups, nor the expression of siRNA from expression vectors comprising U6 or H1 promoters, expressed either as separate self complementary strands or as one, self complementary strand.

Elbashir et al (EMBO J., vol. 20, No. 23, pages 6877-6888, 2001) teach methods of target gene inhibition in embryo lysates comprising siRNA molecules comprising 2'-deoxy and 2'-O-methyl substitutions. Elbashir et al teach a correlation between the placement of 2'-substitutions on the oligonucleotides and retaining siRNA activity (see esp. the abstract on p. 6877, fig. 8 and text on p. 6885).

Fosnaugh et al (US 2003/0143732) teach various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini, and the effect of arrangements of these different modifications on siRNA ability to bind to and inhibit target gene expression in the

presence of RISC. Fosnaugh et al also teach compositions comprising modified and unmodified siRNAs and RISC for target gene inhibition see p. 1, 3-4, 6-9, p. 16 and figures 4 and 5, claim 30).

Morrissey et al (US 2003/0206887) teach various ways of designing and optimizing 2'-O-modifications on siRNA, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and abasic, inverted abasic termini and 5' and 3' capped termini, and the effect of various motifs or arrangements of these 2'substitutuents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA in compositions further comprising RISC (see fig. 4 and 5, page 1, right col., p. 6, right col., p. 9, p. 20-21, claims 20-25).

Tuschl et al (2002/0086356) teach the generation of siRNA molecules from longer dsRNA in the presence of dicer, and the use of 21-23 nucleotide siRNA's to target and inhibit the expression of a target gene in vitro (see the abstract, figures 6, 7, 10-12; pages 1-3, 5, 6 (example 1), pages 10-14 (examples 2-4).

Noonberg (USPN 5,624,803) teach the expression of small inhibitory RNA molecules in mammalian target cells using expression vectors comprising H1 or U6 promoters (see the abstract and figures 11-27, see also col. 13, 15-16, col. 24-25, col. 27, col. 29, claims 2, 3, 7, 14-16).

Baracchini et al (5,801,154) teach the design and use of inhibitory oligonucleotides, including those targeting the 5'UTR of a target gene, which oligonucleotides optionally comprise cholesterol moieties for facilitating target cell entry and which oligonucleotides optionally comprise various modifications for enhancing

oligonucleotide stability and target binding, including 2'-fluoro and alkyloxy modified groups (see esp. col. 6-10, Table III, claims 4, 8, 15).

It would have been obvious to one of ordinary skill in the art to generate small double stranded siRNA molecules to target genomic sequences of HCV because Wands and Wachita teach the polynucleotide sequence of the target HCV genome as well as the design and use of various inhibitory oligonucleotide molecules that target and inhibit HCV in vitro and in vivo, including oligonucleotides that target the 5'UTR of HCV and that specifically target the same sequences that siRNA 5 target. One would have been motivated to use siRNA for HCV target gene inhibition because Fire teaches the advantages of using siRNA molecules compared to other inhibitory oligonucleotides. It would have been obvious to generate smaller siRNA fragments from larger RNA molecules because Tuschl et al, Elbashir et al and Fosnaugh et al teach the generation of these smaller double stranded siRNA molecules upon incubation of larger RNA molecules in the presence of ATP and dicer (as part of the RISC complex). One would have been motivated to generate siRNA fragments between 21-23 nucleotides in length because it was well known in the art that siRNA of this size range successfully inhibit the expression of a target gene of known sequence, including various regions of the HCV genome, as taught previously by Kay et al, Tuschl et al and Elbashir et al. One of ordinary skill in the art would have been motivated to target and inhibit the expression of HCV because this virus is known to infect humans and cause various pathological conditions, and siRNA is well known in the art as a potential therapeutic agent for virus inactivation.

It would have been obvious to incorporate various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini into siRNA molecules for enhancing their target binding and stability, yet minimizing inactivation of the siRNA ability to inhibit target gene expression because Elbashir et al, Fosnaugh et al and Morrissey et al all teach the designing and testing of various arrangements of modified siRNA for their ability to inhibit target gene expression, and Baracchini et al teach the incorporation of various modifications, including 2'-alkyloxy, methoxy or fluoro groups for enhancing oligonucleotide stability. It would have been obvious to incorporate cholesterol moieties onto the oligonucletoides because this has been taught previously by Baracchini for enhancing target cell uptake. One of ordinary skill in the art would have expected that the siRNA modified at appropriate configurations would provide target gene cleavage in the presence of an appropriate target gene sequence and in the presence of appropriately modified siRNA and RISC. One of ordinary skill in the art would have produced various motifs as a matter of design choice and optimizing 2'-O modified motifs within the SiRNA while maintaining its SiRNA activity would have been a matter of design choice. One of ordinary skill in the art would have designed and tested such modification motifs because it was well known in the art at the time of the instant

invention that incorporation of 2'-O-methoxy alky or 2'-deoxy, or 2'-fluoro modifications at appropriate positions within the siRNA allows for enhanced oligonucleotide stability, target binding and the trigger of target gene degradation by RISC. One of ordinary skill in the art would also have been motivated to incorporated 5', and/or 3' caps, including abasic and inverted abasic nucleotide or other terminal well known caps because these modifications were well known in the art to protect oligonucleotides from degradation, as taught previously by Morrissey.

It would have been obvious to one of ordinary skill in the art to express siRNA from expression vectors comprising U6 or H1 promoters because these promoters were well known in the art, as taught by Noonberg et al, for the use in expression vectors for use in mammalian cells and Fire and others in the art have taught expression vectors comprising siRNA for expressing siRNA in target cells following transfection of the target cell with an appropriate expression vector. One of ordinary skill in the art would have been motivated to express these siRNA molecules as separate, self complementary molecules or as a single, self complementary molecule because it was well known in the art that siRNA will self anneal upon appropriate expression in a target cell either as separate strands or as a single, folded strand, and preference would have been a design choice used routinely in the art. One would have expected that these expressed strands would form self complementary double strands in a host or in vitro. Therefore the instant invention as a whole would have been prima facie obvious to one of ordinary skill at the time it was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

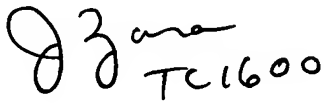
Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
12-12-07



JANE ZARA, PH.D.
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